Journal Club: Pregnancy outcome following maternal exposure to pregabalin may call for concern

Jutzeler, Catherine R ; Cragg, Jacquelyn J ; Warner, Freda M ; Archibald, Jessica ; Thomas, Christine P M ; Elliott, Stacy ; Kramer, John L K

DOI: https://doi.org/10.1212/WNL.0000000000003458

Journal Club: Pregnancy outcome following maternal exposure to pregabalin may call for concern

Catherine R. Jutzeler, PhD
Jacquelyn J. Cragg, PhD
Freda M. Warner, MPH
Jessica Archibald, BSc
Christine P.M. Thomas
Stacy Elliott, MD
John L.K. Kramer, PhD

Correspondence to Dr. Jutzeler: cjutzeler@paralab.balgrist.ch

Owing to its anticonvulsive, analgesic, and anxiolytic properties, pregabalin is used to treat epilepsy, neuropathic pain, and anxiety, respectively. Common side effects include dizziness, lethargy, and drowsiness. Pregabalin is a structural analogue of γ-aminobutyric acid and modulates calcium influx on presynaptic nerve terminals by binding to a subunit on voltage-gated calcium channels.[1]

Evidence from animal studies implicates pregabalin as a potential teratogen.[2,3] Although human data are scarce, pregabalin is a Category C drug: risks cannot be ruled out, but potential benefits may justify the risks of pregabalin during pregnancy. Suggested teratogenic mechanisms include reproductive toxicity, skeletal malformation, neural deficits, spontaneous abortions, growth retardation, and behavioral abnormalities. To shed light on this issue, Winterfeld et al.[4] recently investigated adverse pregnancy outcomes following maternal exposure to pregabalin. Considering the high prevalence of women of childbearing age with neuropathic pain and epilepsy,[5,6] it is important to explore potential teratogenic effects of first-line treatments. Moreover, as pregnant women are considered vulnerable, it is difficult to assess risks during the drug development process. This study provides an elegant example of an observational study used to assess fetal risks resulting from exposure to pregabalin. This work has important implications for clinical practice guidelines for a range of neurologic disorders.

HYPOTHESIS AND DESIGN What is the risk of adverse outcomes following exposure to pregabalin during pregnancy? To answer this important question, Winterfeld et al. performed a multicenter prospective cohort study. A randomized control trial would not be feasible, which makes the use of a prospective observational cohort appropriate. Furthermore, gathering prospective data reduces recall bias associated with retrospective studies.

METHODS The study cohort was defined from individuals within Teratology Information Services databases in several European countries between 2004 and 2013. Exclusion criteria included the intake of any known major teratogen or fetotoxicant, as well as exposure to any treatment for malignancy. The primary outcome of the study was the rate of major birth defects. Two independent and blinded specialists evaluated the data and major birth defects were defined according to standardized classifications. Various secondary endpoints were also defined, such as pregnancy terminations and rates of live births. The primary exposure of interest was pregabalin use during pregnancy, with controls having no exposure to pregabalin or other anticonvulsants. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). This statistical approach is appropriate for binary outcomes (e.g., major birth defect yes/no) and can be used to control for multiple confounders such as smoking, alcohol consumption, maternal age, obstetric history, and concomitant medication use simultaneously.

RESULTS A total of 164 women were exposed to pregabalin. A total of 656 who had not been exposed served as controls. In the treated cohort, pregabalin was primarily administered for neuropathic pain, followed by psychiatric disorders. First trimester pregabalin exposure occurred in the majority (96%) of the sample. Overall, higher rates of major birth defects were found in women exposed to pregabalin during the first trimester of pregnancy (OR 3.0; 95% CI 1.2–7.9). This elevated risk persisted after adjustment for potential confounders (listed above). This multivariable analysis was needed to account for baseline differences noted between the exposed and control group. For example, significantly higher tobacco use was noted in women exposed to pregabalin. Moreover, when examining specific types of major birth defects, rates of CNS malformations were higher in the pregabalin group (OR 6.2; 95% CI 1.4–28.3).

INTERPRETATION These findings strongly suggest that pregabalin should only be considered in women

From ICORD (C.R.J., J.J.C., F.M.W., J.A., C.P.M.T., S.E., J.L.K.K.), School of Kinesiology (C.R.J., F.M.W., J.A., C.P.M.T., J.L.K.K.), and Departments of Psychiatry and Urologic Sciences (S.E.), University of British Columbia, Vancouver, Canada; and Spinal Cord Injury Center (C.R.J.), University Hospital Balgrist, University of Zurich, Switzerland.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

of childbearing age by balancing its potential risks to the child with the benefits to the mother. One major factor is that the debilitating consequences of the condition may necessitate the use of anticonvulsants (e.g., seizures in individuals with epilepsy or severe neuropathic pain).[7] In addition to the pain-relieving effects of pregabalin, a recent study demonstrated a potential benefit of pregabalin on neurologic motor recovery among individuals with acute spinal cord injury.[8]

A study strength is that data were collected prospectively in multiple centers across Europe. The use of prospective data collection on drug exposures during pregnancy removes a major source of bias present in retrospective studies (recall bias). There are, however, some weaknesses to consider, including the following:

1. Relatively small sample size. While this was the largest human study to date exploring pregabalin use during pregnancy, only 164 individuals were exposed during pregnancy. Comparatively, other anticonvulsants have demonstrated negative effects on pregnancy in much larger patient cohorts.[9]
2. There were significant baseline differences in previous spontaneous abortions between the 2 study groups. From the data presented, it is unclear whether or not these women were on pregabalin at the time of spontaneous abortion.
3. In the pregabalin group, 13% were treated with another antiepileptic drug. There were also more complicated medical conditions in the exposed group. The authors adjusted for concomitant treatments with other antiepileptic drugs and some other medications such as antidepressants, but other unadjusted medications could be important confounders. By definition, confounders are associated with both the exposure and outcome, but not on the causal pathway between the exposure and outcome.
4. Accordingly, another potential confounder could be the indications for the anticonvulsant medications, including pain or epilepsy. Though there is mixed evidence, there are some data suggesting that epilepsy can increase the risk of adverse pregnancy outcomes, even in epileptic women not exposed to anticonvulsants.[10] There is also some evidence to suggest that stress, which is highly correlated with pain, can increase the risk of birth defects.[11]
5. Interaction effects of the drugs were not included in the analysis. From a pharmacologic point of view, drug–drug interactions are of great importance and thus should not be neglected. One exclusion criterion was maternal exposure to any known major teratogen or fetotoxicant. However, some of the reported concomitant drugs, such as topiramate and valproic acid, are known to be highly teratogenic (evidence for positive evidence of risk [Category D] or contraindicated in pregnancy [Category X]).[12] Taken together with the aforementioned concerns, it is difficult to completely discern the teratogenic effects of pregabalin from other drugs or interaction effects.
6. There was a mixture of methodology used to ascertain outcomes. Follow-up was obtained via a telephone interview or mailed questionnaire to the patient or health care professional. This issue would be particularly problematic if it differed by pregabalin use (i.e., nondifferential misclassification of outcome).
7. A dose response—one of the criteria for causality—was not observed, as with several other teratogens.[13]
8. Cases and controls were women who themselves or whose physician contacted one of the teratology centers. Thus, a selection bias in both groups cannot be ruled out.

Women of childbearing age contemplating a pregnancy and undergoing treatments for neuropathic pain, epilepsy, or psychiatric disorders represent a dilemma for treating physicians: is treatment with pregabalin or other anticonvulsants worth the risk of harm to the child? With their article, Winterfeld et al. provide evidence that antiepileptic drugs carry teratogenic potential. As this is the only current evidence on the matter, pregabalin should only be given to women of childbearing age after an informed decision, weighing the benefits and risks. Furthermore, all women requiring the use of antiepileptics of any kind should be stringently monitored during pregnancy.

AUTHOR CONTRIBUTIONS

Dr. Jutzeler: drafting/revising the manuscript, analysis or interpretation of data. Dr. Cragg: drafting/revising the manuscript, analysis or interpretation of data. M.P.E. Warner: revising the manuscript, interpretation of data. J. Archibald: revising the manuscript. C.P.M. Thomas: revising the manuscript. Dr. Kramer: drafting/revising the manuscript, analysis or interpretation of data.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res 2007;73:137–150.
2. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Fetal growth restriction and birth defects with newer and older antiepileptic drugs during pregnancy. J Neurol 2014;261:579–588.

3. Etemad L, Mohammad A, Mohammadpour AH, Vahdati Mashhadi N, Moallem SA. Teratogenic effects of pregabalin in mice. Iran J Basic Med Sci 2013;16:1065–1070.
4. Winterfeld U, Merlob P, Baud D, et al. Pregnancy outcome following maternal exposure to pregabalin may call for concern. Neurology 2016;86:2251–2257.
5. McHugh JC, Delanty N. Epidemiology and classification of epilepsy: gender comparisons. Int Rev Neurobiol 2008; 83:11–26.
6. Hall GC, Carroll D, Parry D, McQuay HJ. Epidemiology and treatment of neuropathic pain: the UK primary care perspective. Pain 2006;122:156–162.
7. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life: review and implications. Neurology 2007;68:1178–1182.
8. Cragg JJ, Haefeli J, Jutzeler CR, et al. Effects of pain and pain management on motor recovery of spinal cord-injured patients: a longitudinal study. Neurorehabil Neural Repair 2016;30:753–761.
9. Holmes LB, Wyszynski DF, Lieberman E. The AED (antiepileptic drug) pregnancy registry: a 6-year experience. Arch Neurol 2004;61:673–678.
10. Battino D, Tomson T. Management of epilepsy during pregnancy. Drugs 2007;67:2727–2746.
11. Carmichael SL, Shaw GM, Yang W, Abrams B, Lammer EJ. Maternal stressful life events and risks of birth defects. Epidemiology 2007;18:356–361.
12. Ornoy A. Valproic acid in pregnancy: how much are we endangering the embryo and fetus? Reprod Toxicol 2009;28:1–10.
13. Shepard TH. Dose response in human teratology. Teratology 2002;65:199–200.

Journal Club: Pregnancy outcome following maternal exposure to pregabalin may call for concern

Catherine R. Jutzeler, Jacquelyn J. Cragg, Freda M. Warner, et al.

Neurology 2017;88;e5-e7
DOI 10.1212/WNL.0000000000003458